THE BLOOD PICTURE IN HODGKIN'S DISEASE*

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DISCUSSION *by Ernest S. du Bray, M. D., San Francisco; John J. Sampson, M. D., San Francisco; Munford Smith, M. D., Los Angeles.*

SINCE the publication of Bunting's work in 1911 [1] and 1914,[2] analyzing a series of blood counts in Hodgkin's disease, our interest has been directed toward the importance of the blood picture in this disease. We use the term "Hodgkin's disease" in this paper instead of the newer nomenclature because of the fact that long usage distinguishes this disease from lymphosarcoma. Bunting's work tended to show that it is possible to divide cases of Hodgkin's disease into two distinct groups, according to the differential count of the leukocytes. The first group, consisting of cases of one year or less duration, showed a normal or decreased percentage of polymorphonuclear neutrophils. The second group, those cases of longer than one year duration, showed a leukocytosis, running in one instance to 100,000 leukocytes per cubic millimeter. The leukocytosis present was found to be made up of a neutrophilic percentage between 72 and 90 per cent. The most striking feature of the differential count was the increase in the transitional leukocyte, a large mononuclear cell with indented, irregular nucleus and fine azurophil granulation with Wright's stain. These cells were found increased in both groups. The lymphocytes might be increased in the very early cases, but tended to decrease in the later cases, varying from 7.6 to 3.4 per cent. The eosinophil count was found to be variable, never high except in rare cases. The basophils were increased in early cases, later tending to disappear from the circulation. Platelets were always increased in both groups.

The analysis in this report is patterned after Bunting's analyses. The chief reason for publishing these data is to again call attention to the value of carefully made blood counts in this disease and to emphasize the fact that an increase in the eosinophilic percentage in the differential count is not an important and a constant feature in the blood picture. Many students and practitioners hold this idea, apparently having been taught it at some time in their careers. There are certain exceptional cases of Hodgkin's disease that show a remarkable eosinophilia, as, for example, the following case from the male medical ward in the University of California Hospital. An average of ten blood counts shows this composite leukocyte and differential count: Red cells, 4,874,000; hemoglobin, 88.3 per cent; white blood cells, 43,875; polymorphonuclear neutrophils, 14; polymorphonuclear eosinophils, 65.5; polymorphonuclear basophils, 1.2; lymphocytes, 11.3; and monocytes, 8. One or two of the differential counts in this individual showed as high as 80 per cent eosinophils. There was an extensive erythema and infiltration of the skin in this patient.

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ANALYSIS OF TABLES

An analysis of Table 1 shows twenty cases on whom ninety-three blood counts were made. There are twenty-one composite counts entered in this table, but Case No. 26716 appears twice, having two sets of blood counts in two different entries. The average hemoglobin and average red cell count for the group shows a moderate secondary anemia. The average white count is 11,728, slightly above the usual normal, but still within the higher limits of normal. The polymorphonuclear eosinophil, basophil, and lymphocyte ratios are within normal limits, but the monocytes, 10.2 per cent, are increased. The large mononuclear cell and the transitional are grouped together in this study under the term "monocytes." We have been unable to find any definite criteria to differentiate between these two types of cells, so we group them under the term "monocyte." The normal percentage of monocytes is taken as about 6 to 8 per cent of all the leukocytes.

Table 2, comprising cases of more than one year's duration and up to thirteen years, in one case shows an average white cell count of 14,350 white cells per cubic millimeter. This count is an average of eighty counts made in twenty patients. In this group it will be noted that the polymorphonuclear ratio averages 68.4 per cent, not much higher than Table 1. A few cases with low neutrophil count serve to bring down the percentage. The eosinophil count averages 2 per cent, the lymphocyte count 20.7 per cent, and monocytes 8.5 per cent. The monocyte count is only slightly increased in this group.

Table 3 is composed of two small groups divided as to time limits into Group "A," one year or less; and Group "B," more than one year. These cases have had very carefully performed white blood counts with the differential count checked by the author. These groups are small, but are worth recording as several counts have been made in each case and a composite average recorded in the table. It is interesting to note that in Group "A," of one year or less duration, the white cell count and differential is within normal limits with the exception of the monocytes, which are increased. In Group "B," cases of more than one year duration, the white cell count averages 11,500, a slight increase with an increase in the percentage of polymorphonuclear neutrophils at the expense of a decrease in the lymphocyte percentage. The monocyte count is 10 per cent, the same as Group "A." The platelets and reticulated cell counts have been recorded in Table 3. The platelets are not particularly increased in the averages shown. By the method used [3] 300,000 falls well within the normal range. The reticulocyte count in Group "A" indicates that the marrow is fairly active in the early cases. In Group "B" it appears to indicate some "falling

TABLE 1.—*Cases of Apparent Duration Under One Year*

Sex and Case No.	Age	Diagnosis by Biopsy or Autopsy	Apparent Duration of Disease	Number of Blood Counts	Hgb.	Erythrocytes	White Blood Cells	N	E	Bas.	L	M	Plates.
M 8127	17	B. A.	1 yr.	4	81	3,630,000	17,510	82	1.2	.3	9.	7.4	
M 2869	33	B.	6 mos.	2	70	5,200,000	9,700	85	3.		8	4	Number appears normal
F 8950	54	B.	8 mos.	2	85	4,280,000	9,300	75	1.	.5	19	4.5	
M 13876	22	B. A.	1 yr.	9	50	3,600,000	12,830	20	.7	.5	77.2	1.6	
M 18468	42	B.	6 mos.	6	47	3,130,000	10,400	80	1.	.1	15.7	3.2	
M 12699	50	B.	7 mos.	3	87	4,960,000	6,000	52	7.	.7	26.3	14.	
M 25746	41	B.	8 mos.	5	71	3,600,000	6,100	74	1.2	.2	15.	9.6	
M 25751	34	B.	5 mos.	3	90	5,020,000	7,150	51	2.	.7	37.	9.3	
M 22992	40	B.	9 yrs.	2	75	3,952,000	9,150	79	2.	0.	14.	5.	
M 10851	29	B.	4 mos.	1	85	4,352,000	13,800	46	14.	0.	25.	15.	
M 33396	23	B. A.	3 mos.	11	62	3,517,000	17,400	85.5	0.	.1	8.3	6.1	592,000
F 12909	33	B. A.	1 yr.	2	95	4,760,000	5,650	75.	1.	0.	19.	5.	
M 16599	39	B.	10 mos.	9	76.5	3,898,000	7,000	80.	3.1	.2	9.	8.7	
F 46234	62	B.	9 mos.	1	80.	4,430,000	17,840	85.6	0.	0.	9.	5.4	
F 23656	65	B.	6 mos.	2	94.	5,420,000	7,800	67	1.	.7	26.	5.3	
M 26716	21	B. A.	11 mos.	5	48.5	3,724,000	44,250	88	2.2	.2	4.2	5.4	
M 26716	21	B. A.	1 yr.	4	49	3,095,000	84,960	89	3.2	0.	4.5	3.3	
M 13760	24	B. A.	6½ mos.	11	50	4,080,000	33,300	89.2	.2	0.	4.9	5.7	
M 43370	47	B. A.	4 mos.	3	89	4,625,000	5,640	63.3	2.	.1	23.3	11.3	
M 20334	42	B.	5 mos.	2	83	4,900,000	5,400	53	4.5	1.	28	12.5	
M 8226	22	B.	8 mos.	6	48	3,549,000	9,220	65.2	1.5	.3	24.	9.	
				93	72	4,200,000	11,728	60.4	2.4	.4	26.6	10.2	

B—Biopsy A—Autopsy N—Neutrophils E—Eosinophils Bas—Basophils
L—Lymphocytes, large and small M—Monocytes which include large mononuclears and transitionals

off" in the regenerative power of the bone marrow in those cases beyond one year in duration.

SUMMARY

The results of our blood studies in Hodgkin's disease conform in a general way to the results and conclusions worked out by Bunting several years ago. In our results it is difficult to be sure of the duration of the disease from the history obtained from the patient. In Table 1 there are undoubtedly some inaccuracies with respect to the duration of the disease, as the onset is nearly always insidious and the patient is not aware of the disease until it has been progressing for several weeks. It is very important to realize that occasionally leukemia-like blood pictures may occur in Hodgkin's disease, as seen in this patient at the age of thirty-six who entered the male medical ward at the University of California Hospital from the medical clinic with a leukocyte count of 36,200; polymorphonuclears, 14 per cent; lymphocytes, 86 per cent. From his history the duration appeared to be about eight months. His blood count after entry to the hospital was: hemoglobin, 75; red blood cells, 4,460,000; white cells, 25,000; polymorphonuclears, 35; large lymphocytes, 2; small lymphocytes, 60; and monocytes, 3 per cent. This patient had a paraplegia, and an x-ray film of the spine showed nodules in one of the lower dorsal vertebrae.

CONCLUSIONS

This analysis substantiates the idea that later in the disease, beyond the first year, the leukocyte count tends to become increased, with an increase in the polymorphonuclear leukocytes. Also there is an average and fairly constant increase

TABLE 2—*Cases of Apparent Duration of One Year or More*

Sex and Case No.	Age	Diagnosis by Biopsy or Autopsy	Apparent Duration of Disease	Number of Blood Counts	Hgb.	Erythrocytes	White Blood Cells	N	E	Bas.	L	M	Plates.
F 21763	54	B. A.	3½ yrs.	10	50	3,215,000	11,196	85.	2.7	.9	1.8	10.6	
M 23730	22	B.	3 yrs.	5	60	3,591,000	5,240	70.	1.	.0	20.6	8.4	
F 47044	45	B.	4 yrs.	1	79	4,100,000	8,680	57.	7.	2.	26.	8.	
M 47336	26	B.	18 mos.	1	65	4,010,000	16,850	16.	4.	0.	72.	8.	
M 47322	46	B.	14 mos.	1	80	4,150,000	9,400	72.	2.	0.	19.	7.	
M 24678	10	B. A.	18 mos.	5	83	4,606,000	15,740	80.	.7	.3	10.	9.	
M 14490	24	B. A.	14 mos.	11	50	4,084,000	33,000	89.	.2	0.	5.	5.8	
F 16034	25	B. A.	3 yrs.	1	65	3,000,000	10,600	66.	0.	0.	24.	10.	
M 38003	15	B. A.	6 yrs.	1	35	2,240,000	35,500	89.	0.	0.	5.	6.	
M 38427	21	B. A.	21 mos.	2	42	2,943,000	22,500	82.5	2.5	0.	10.	5.	
F 31786	30	B.	8 yrs.	5	75	4,010,000	10,730	81.	2.5	.2	11.	5.3	
M 46455	8	B. A.	2 yrs.	8	37	2,041,000	5,600	87.	.4	0.	6.	6.6	405,900
M 10391	47	B.	2 yrs.	5	50	3,141,000	10,100	66.	4.6	.6	22.	6.8	
F 13704	37	B.	16 mos.	2	65	4,320,000	15,900	86.5	.5	.5	9.5	3.	
F 1521	27	B.	1½ yrs.	1	55	4,488,000	14,800	60.	1.	0.	30.	10.	
F 598	52	B.	5 yrs.	1	90	5,240,000	12,000	47.	8.	0.	36.	9.	
M 33735	40	A.	13 yrs.	7	61	3,220,000	20,900	83.	0.	0.	13.5	3.5	
M 25556	43	B.	1 yr. 9 mos.	10	60	3,200,000	3,500	57.6	1.4	1.	25.	15.	432,000
M 16219	22	B.	4 yrs.	2	90	4,500,000	11,300	22.5	.2	.5	62.	15.	
F 16980	35	B.	5 yrs.	1	75	3,592,000	13,500	72.	5.	0.	6.	17.	
				80	63	3,684,550	14,350	68.4	2.	.02	20.7	8.5	

B—Biopsy A—Autopsy N—Neutrophils E—Eosinophils Bas—Basophils
L—Lymphocytes, large and small M—Monocytes which include large mononuclears and transitionals

in the mononuclear cells. For some reason our platelet counts are not high, as other authors have found them. This is a matter for further investigation. The eosinophil count averages about normal or below but may occasionally be very high, reaching in one instance 80 per cent of the total leukocytes.

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REFERENCES

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DISCUSSION

ERNEST S. DU BRAY, M. D. (490 Post Street, San Francisco).—I think it is safe to say that Doctor Falconer has brought together in the foregoing paper the largest and most completely studied group of cases of Hodgkin's disease, from the blood standpoint, that has appeared in the American medical literature since the classic contributions of Bunting. It is rather significant that this study confirms Bunting's work in the chief essentials. Although it is true the blood picture alone cannot be relied upon absolutely to make the diagnosis in a border-line case, nevertheless it is of value in offering strong corroborative evidence in cases of general glandular enlargement. Such conditions as lymphosarcoma, tuberculosis, leukemia, and infectious mononucleosis are among the frequent confusing disturbances that come to mind in the differential diagnoses of glandular enlargement. To be sure the biopsy is nowadays resorted to early, but at times even the pathologist hesitates to go on record positively from a study of the gland tissue.

In a general way it can be said that Hodgkin's disease usually presents a secondary anemia which increases as the disease progresses. The white blood count may be normal early in the course of the illness, but later a moderate leukocytosis between 10,000 and 20,000 usually appears. The polymorphonuclear neutrophils gradually increase and are found

TABLE 3.—*Groupings Based on Time Limits**

Sex and Case No.	Apparent Duration of Disease	White Blood Count	N	E	B	L	M	Plates.	Retic. Reds
			GROUP "A"—*Less Than One Year*						
F 1	1 yr.	5,650	73	2	0	13	10	312,000	2.
F 2	10 mos.	6,400	50	6	1	34	9	160,000	1.2
M 6	11 mos.	7,850	80	1	0	12	7	420,000	2.6
M 4	1 yr.	10,400	77	1	0	13	9	260,000	4.4
F 8	8 mos.	9,000	36	2	1	44	17	268,000	.8
M 9	1 yr. 11 mos.	6,600	65	3	0	20	12	368,000	.6
M 13	7 mos.	9,550	73	1	0	23	3	480,000	2.
		7,921	65	2	.3	23	10	324,000	2.3
			GROUP "B"—*More Than One Year*						
M 3	18 mos.	9,900	80	0	0	8	12	325,000	.8
M 5	2 yrs.	6,350	65	1	0	10	24	184,000	.2
F 7	4 yrs.	9,450	70	2	0	22	6	310,000	.4
M 10	2 yrs.	6,920	70	2	0	23	5	254,000	1.2
M 12	1 yr.	32,000	79	3	1	10	7	532,000	3.7
M 11	3 yrs.	9,600	80	3	0	10	7	164,000	1.2
M 14	1 yr. 4 mos.	6,300	72	1	0	19	8	355,000	.0
		11,503	74	2	.1	15	10	303,428	1.1

*Special counts checked by author done in the Hematology Clinic.
N—Neutrophils E—Eosinophils Bas—Basophils L—Lymphocytes, large and small
M—Monocytes which include large mononuclears and transitionals Plates.—Platelets Retic. Reds—Reticulated red cells

commonly between 70 and 90 per cent, with an absolute increase in the transitional cell, which Doctor Falconer includes in his monocyte group. Bunting, it will be recalled, emphasized the absolute increase in the transitional cell even in the early cases.

Most observers have noted a definite increase in the platelets, but as the exact numerical determination of platelets depends considerably on the method used, this may partially account for this apparent discrepancy in that the platelets in this present study appeared about within normal limits. Another feature, with reference to the platelets that some observers have noted, was the conspicuous presence of giant platelets in considerable numbers. The presence of marked eosinophilia has undoubtedly been overstressed as an important feature of the blood picture. It may be said, however, that it does occur, particularly with either one of two conditions existing, viz.: widespread skin involvement or a necrosis in lymph glands.

In conclusion, I would like to compliment Doctor Falconer on the concise and yet complete way the above study is presented. He has again shown that the Oslerian method of an intense study of a single phase of a well-known disease is not without profit.

JOHN J. SAMPSON, M. D. (490 Post Street, San Francisco).—Doctor Falconer, as Doctor du Bray has pointed out, has rendered a genuine service in stabilizing our knowledge of the changes that take place in the blood in Hodgkin's disease.

I believe that there are some remarkable variations in morphology that are worthy of mention, in addition to the changes in total and relative numbers of blood cells that Doctor Falconer summarizes. The monocytes (large mononuclear leukocytes or endothelial leukocytes), in my experience have often been found to assume the same forms frequently seen in subacute bacterial endocarditis, namely, increase in size, vacuolization, and definite large pseudopod formation.

The platelets, especially during the phase of the disease in which they are increased in number, have been observed to be increased in size, occasionally as much as twenty microns. Such platelets are more liable to be elongated along a single meridian.

There is still a difference of opinion as to recognition of Hodgkin's disease as a separate entity in contrast to its possible classification in a general lymphoblastoma group. Transitional cases occasionally appear which seem to link it with either lymphosarcoma on one extreme or lymphatic leukemia on the other.

I believe it is wise to withhold the decision as to which of these conclusions may be correct, and therefore still reserve the possibility of interpreting these blood changes in another light than that they may be characteristic of Hodgkin's disease, as a distinct clinical entity.

MUNFORD SMITH, M. D. (1105 Roosevelt Building, Los Angeles).—Doctor Falconer has presented a large, interesting group of cases of Hodgkin's dis-

ease, thoroughly studied from the standpoint of the blood picture. It well illustrates that there is a slightly higher white cell count and increased polymorphonuclear neutrophil count in the older cases; also, that there is rarely an eosinophilia in Hodgkin's disease, which is an incorrect point of differentiation so frequently insisted upon.

At the time that this paper was presented to me I was particularly interested in the differentiation between Hodgkin's disease and tuberculous adenitis, having recently seen several cases where a question had arisen. I had made a partial survey of the literature, but had found nothing so well covered as in Doctor Falconer's paper. Biopsy still remains the method of choice to differentiate between several conditions which may be confused with Hodgkin's disease.

SYSTEMIC BLASTOMYCOSIS*

REPORT OF CASES

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THE term "blastomycosis," in its broad sense, includes all diseases caused by yeast-like fungi, that is, fungi which appear in the lesions as round or oval cells, sometimes budding, but usually without mycelium. These fungi are generally called blastomycetes, and include members of several genera.

However, in this country the tendency has been to restrict the term "blastomycosis" to infection with *Blastomyces dermatitidis* (Gilchrist and Stokes) and there seems to be constant effort to designate otherwise infections with related but distinct organisms. This is particularly true in California, where infection with *Coccidioides immitis* is so frequently seen. While several cases of coccidioidal infection have been reported in the literature as systemic blastomycosis, they were so reported because the organisms were not differentiated, and the true nature of the infection was not recognized.

CASTELLANI'S CLASSIFICATION OF BUDDING FUNGI

Castellani [1] has recently proposed a new classification of the yeast-like or budding fungi, based on the presence or absence of mycelium, and presence or absence of ascospores, which includes families of both Ascomycetes and Fungi imperfecti.

(*a*) Family Saccharomycetaceae, with budding cells, asci and ascospores, but no mycelium in culture.

(*b*) Family Endomycetaceae, with budding cells, asci and ascospores with mycelium in culture.

(*c*) Family Cryptococcaceae, with budding cells (blastospores), no asci and no mycelium in culture.

(*d*) Family Oösporaceae, with budding cells, no asci but mycelium in cultures.

He creates a new genus, which he calls Blastomycoides, under Family Oösporaceae, in which he places three species: 1. *Blastomycoides dermatitidis,* synonym—*Blastomyces dermatitidis* (Gilchrist and Stokes). 2. *Blastomycoides immitis,* synonym—*Coccidioides immitis* (Rixford and Gilchrist). 3. *Blastomycoides tularensis* (Castellani). He defines the genus Blastomycoides as: "Oösporaceae appearing in the lesions as large roundish cells from eight to twenty microns in diameter, or larger, with the protoplasm containing a number of well-marked granules or spherules, and with a membrane showing a well-defined double contour: in dextrose agar cultures a large amount of mycelium is present." There are slight cultural differences of the three species when grown on mannitol, glucose, lactose and galactose agar.

In justifying his reasons for placing Coccidioides in the above genus, he contends that "the spherules found in the large round cells are not ascospores, but are protoplasmic granules, and that in culture, when one of the organisms produces a bud, which later becomes a filament, the same granules are seen in the mycelium." He also states that Coccidioides grows in cultures as a saccharomyces type which reproduces by budding, and a filamentous type.[2] He moves the species *Coccidioides immitis,* genus Coccidioides, family Endomycetaceae, class Ascomycetes, to genus Blastomycoides, species *Blastomycoides immitis,* family Oösporaceae, class Fungi imperfecti.

Thus, he also moves *Cryptococcus dermatitidis,* synonym—*Blastomyces dermatitidis* (Gilchrist and Stokes) from genus Cryptococcus, family Cryptococcaceae to family Oösporaceae, genus Blastomycoides, species *Blastomycoides dermatitidis.*

We agree with Castellani on the value of a better classification, but do not feel that the species *Coccidioides immitis* should be grouped in genus Blastomycoides, even though it has cultural characteristics similar to others of this genus. He apparently has arrived at this classification of the organism wholly upon the cultural characteristics without regard for the generally accepted ideas of the morphology of the organisms in the lesions, that is, he does not agree with other observers on the method of reproduction of Coccidioides in tissues, viz., multiplication by endosporulation with complete absence of budding.

Therefore we feel that *Coccidioides immitis,* in spite of cultural similarity, is not sufficiently closely related to *Blastomyces dermatitidis* to be placed in the same genus.

The two cases which we report as generalized or systemic blastomycosis are caused by organisms of the species *Blastomyces dermatitidis* (Gilchrist and Stokes), or *Blastomycoides dermatitidis* (Castellani).

NATURE OF BLASTOMYCOSIS INFECTION

Little is known of the source and manner of infection. In some cases the primary focus has

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